



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 157766.7 SB		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/IL2005/000043		International filing date (<i>day/month/year</i>) 13.01.2005		Priority date (<i>day/month/year</i>) 15.01.2004
International Patent Classification (IPC) or national classification and IPC INV. C07F9/6584 C07F9/113 A61K31/661				
Applicant BIOLAB LTD.				
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> <i>sent to the applicant and to the International Bureau</i> a total of 10 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand 15.11.2005		Date of completion of this report 20.04.2006		
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized officer Seitner, I Telephone No. +31 70 340-2389 		

10/506453

INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY

International application No.
PCT/L2005/000043

AP20 Rec'd PCT/PTO 14 JUL 2006

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-22 as originally filed

Claims, Numbers

1-51 received on 21.11.2005 with letter of 14.11.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/L2005/000043

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 30,35,43,44,49,50,51 (in part)
because:
 - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 30,35,43,44,49,50,51 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet
 - ☒ the claims, or said claims Nos. 30,35,43,44,49,50,51 are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☒ no international search report has been established for the said claims Nos. 30,35,43,44,49,50,51 (in part)
 - ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
 - ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
 - ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/IL2005/000043

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-42,45-49
	No: Claims	43,44,50,51
Inventive step (IS)	Yes: Claims	
	No: Claims	1-51
Industrial applicability (IA)	Yes: Claims	1-51
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

10/586056

10/586056

International application No.

PCT/IL2005/000043

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 30,35,43,44,49,50,51 relate to formulae (3), (4), (5), (6) in which the substituents Z, R2, and R4 are defined by reference to a desirable characteristic or property, namely "protecting group" and "hydrophobic group".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Moreover, the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible.

Consequently, the search has been restricted to the compounds according to formulae (3)-(6) as exemplified in the description and the use of example 5a according to claims 50 and 51.

A complete international preliminary examination of the present application is limited to those parts of the claims for which a complete international search report was established (Rule 66.1(e) PCT). It should in particular be understood that any positive statement as to novelty and/or inventive step exclusively relates to said limited subject-matter.

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

Reference is made to the following documents:

- D2: DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHIBAGAMI, MOTONARI ET AL: "Preparation of sphingolipids for pharmaceuticals and cosmetics" XP002323215 retrieved from STN Database accession no. 2004:17805
- D5: RAMSTEDT, BODIL ET AL: "Comparison of the biophysical properties of racemic and D-erythro-N-acyl sphingomyelins" BIOPHYSICAL JOURNAL, 77(3), 1498-1506 CODEN: BIOJAU; ISSN: 0006-3495, 1999, XP002323211
- D6: HANS-PETER DEIGNER AND BEATRIX FYRNYS: "Rapid synthesis of 2-desoxy-2-amino-3-phosphocholine-glyceric acid-alkylester, 1-alkyl-1-desoxy- and 1-o-alkyl-2-desoxy-2-amino-sn-glycero-3-phosphocholines, -3-phospho-N,N'-dimethylethanolamine and -3-phospho-Fmoc-serine-methylester" CHEMISTRY AND PHYSICS OF LIPIDS, vol. 61, 1992, pages 199-208, XP002323214
- D7: H.P. DEIGNER AND B. FYRNYS: "Synthesis of [32P]-labelled 1-O-alkyl-2-desoxy-2-amino-sn-glycero-3-phosphocholines" JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMCEUTICALS, vol. 34, no. 2, 1994, pages 185-190, XP008045160
- D8: C.M. THOMPSON ET AL: "Synthesis, Configuration, and Chemical Shift Correlation of Chiral 1,3,2-Oxazaphospholidin-2-ones Derived from L-Serine" JOURNAL OF ORGANIC CHEMISTRY, vol. 55, 1990, pages 111-116, XP002323263

D9: ZHENG-JIE HE ET AL: "Synthesis of novel optically active cyclic phospholipid conjugates of tegafur and uridine starting from L-serine" PHOSPHORUS, SULFUR AND SILICON, vol. 160, 2000, pages 223-232, XP008045147

V.1. Novelty:

Present claim 43, 44, 50, and 51 relate to compounds of formula (5) and their pharmaceutical use and composition. Claim 43 comprises a proviso with respect to a substituent R^2 which is however not present in the formula (5) itself. Since the meaning of the proviso is not clear, it cannot be taken into consideration, when assessing the novelty of the compounds. Documents D2 and D5 disclose the example (5a) of the present description as well as its pharmaceutical use. In this context, it has to be furthermore noted that a product is not rendered novel merely by the fact that it is produced by means of a new process: the use of a different parameter, i.e. by reference to a new process, for defining a known product does not confer novelty on the product itself.

Therefore, the subject-matter of claims 43, 44, 50, and 51 is not novel (Article 33(2) PCT).

The compounds of formulae (1), (3), (4), (6) and the processes for their preparation have not been disclosed in the available prior art:

Therefore, the subject-matter of claims 1-42, 45-49 is novel (Article 33(2) PCT).

V.2. Inventive Step:

The subject-matter of claims 1-42, 45-49 does not involve an inventive step in the sense of Article 33(3) PCT, and therefore the criteria of Article 33(1) PCT are not met:

The reaction of L-serine with POCl_3 to yield oxazaphospholane which is then used as starting material for the preparation of various phospholipid derivatives is a method very well known from the prior art (see D6-D9). It would therefore have been obvious to the skilled person to use this method for preparing the sphingomyelin derivatives of the present application.

The subject-matter of claims 43, 44, 50, 51 which lacks novelty, does not offer a basis for acknowledging an inventive step.

Thus, the subject-matter of present claims 1-51 cannot be considered as involving an inventive step in the sense of Article 33(3) PCT).

V.3. Industrial Applicability:

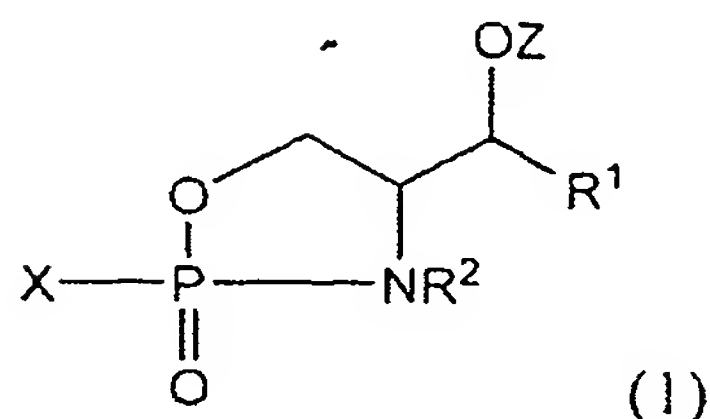
The present application relates to a process for preparing sphingomyelin-derivatives and the intermediates used in this process. The subject-matter of claims 1-51 is therefore considered as industrially applicable (Article 33(4) PCT).

AP20 Rec'd PCT/PTO 14 JUL 2006

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CLAIMS:

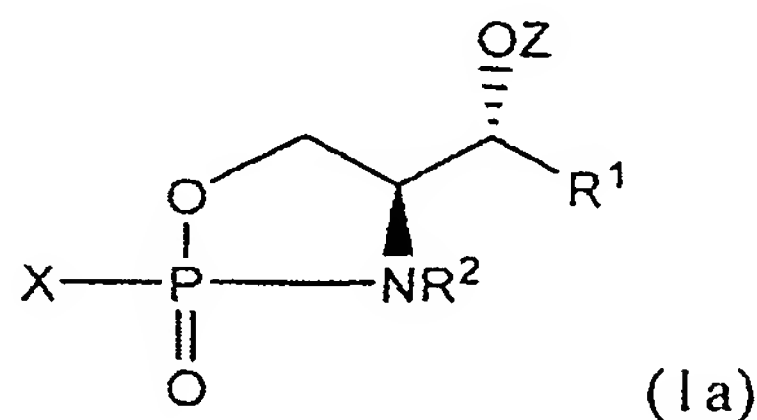
1. An oxazaphospholane compound of the following formula (1):



wherein R^1 represents a C_1 - C_{24} aliphatic moiety which may be saturated or unsaturated, branched or linear chain, optionally containing an aliphatic ring, R^2 represent a hydrogen atom or hydrophobic group, Z represents a protecting group and X represents a leaving group.

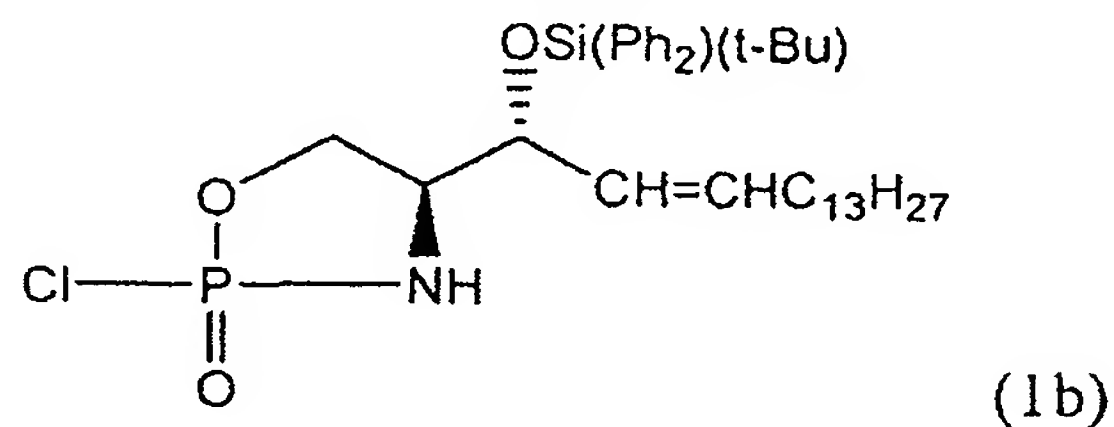
2. The oxazaphospholane compound of Claim 1, wherein R^2 represents a hydrogen atom or a C_1 - C_{24} aliphatic moiety selected from saturated or unsaturated, branched or linear aliphatic chain, said aliphatic chain optionally containing an aliphatic ring; the aliphatic chain and aliphatic ring optionally substituted with one or more substituents containing a heteroatom selected from oxygen, halogen, nitrogen and sulfur.
3. The oxazaphospholane compound of Claim 1 or 2, wherein R^1 represents a C_8 - C_{24} aliphatic moiety.
4. The oxazaphospholane compound of Claim 2 or 3, wherein R^2 represents a hydrogen atom or a saturated or unsaturated C_8 - C_{24} aliphatic moiety.
5. The oxazaphospholane compound of Claim 4, wherein R^2 represents a hydrogen atom.
6. The oxazaphospholane compound of any one of Claims 1 to 5, wherein X represents a halogen atom.
7. The oxazaphospholane compound of Claim 6, wherein X represents Cl.

8. The oxazaphospholane compound of any one of Claims 1 to 7, wherein Z represents a $\text{Si}(\text{R}^5)_3$ group in which R^5 may be the same or different in the same compound and represent a $\text{C}_1\text{-C}_6$ branched or straight alkyl group or an aryl group.
9. The oxazaphospholane compound of Claim 8, wherein said Z represents $\text{Si}(\text{Ph})_2(\text{t-Bu})$.
10. An oxazaphospholane compound of the following formula (1a):



being the 2S,3R stereoisomer of the compound of any one of Claims 1 to 9, wherein R^1 , R^2 , X and Z are as defined.

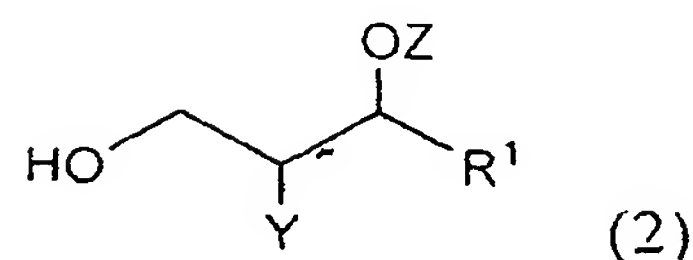
11. The oxazaphospholane compound of any one of Claims 1 to 8, wherein R^1 is (*E*)- $\text{CH}=\text{CHC}_{13}\text{H}_{27}$, R^2 is hydrogen, X is Cl and Z is $\text{Si}(\text{Ph})_2(\text{t-Bu})$.
12. The oxazaphospholane compound of any one of Claims 1 to 8, wherein R^1 is (*E*)- $\text{CH}=\text{CHC}_{13}\text{H}_{27}$, R^2 is hydrogen, X is substituted with the group $-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}^+(\text{CH}_3)_3$.
13. The oxazaphospholane compound of any one of Claims 1 to 8, being the (*E*)-geometrical isomer of the compound of the following formula (1b):



14. The oxazaphospholane compound of any one of Claims 1 to 13, being an isolated stable compound.
15. A process for the manufacture of an oxazaphospholane compound of formula (1) as defined in any one of Claims 1 to 14, the process comprises reacting a

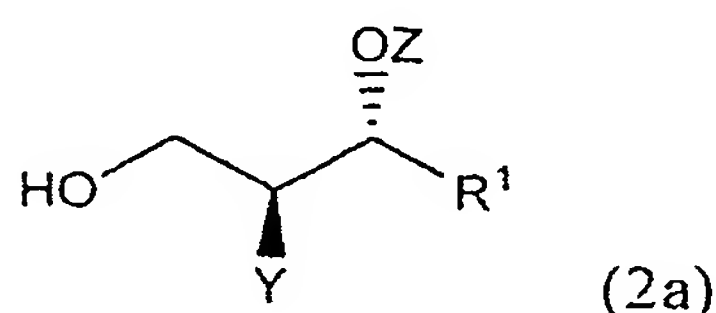
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phosphorylating reagent with a 3-O-protected sphingoid compound of the following formula (2):



wherein R¹, Z and X are as defined and Y is an amine or an amino group.

16. The process of Claim 15, comprising reacting said phosphorylating reagent with a 2S, 3R stereoisomer of the following formula (2a):

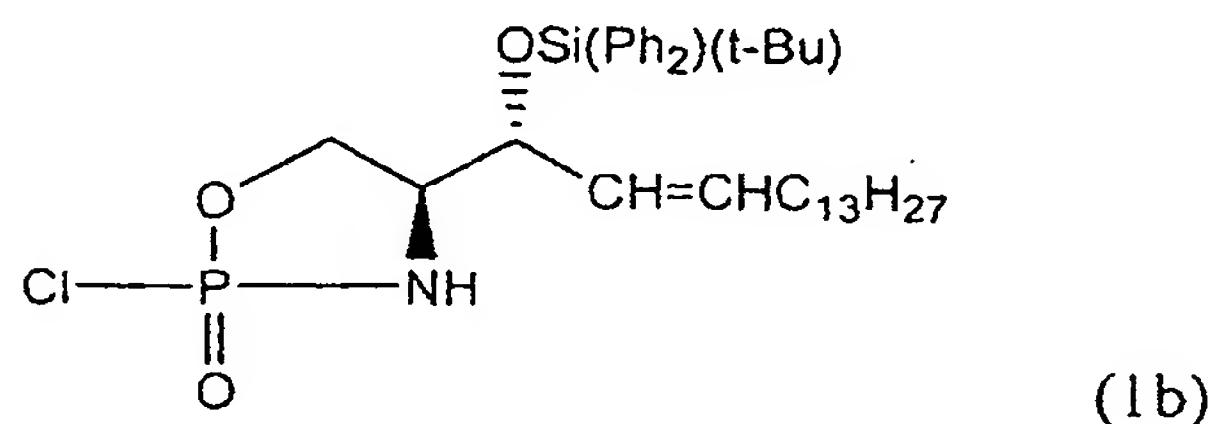


17. The process of Claim 15 or 16, wherein said phosphorylating reagent is reacted with the protected sphingoid compound in which Y represents NH₂.

18. The process of any one of Claims 15 to 17, wherein said phosphorylating reagent is selected from POW₃, wherein W represents a halogen atom; an ethylene chlorophosphite; a methyl phosphodichloridite; a chloro-N,N-diisopropylaminomethoxophosphite; or [(isopropyl)₂N]₂POCH₂CH₂CN.

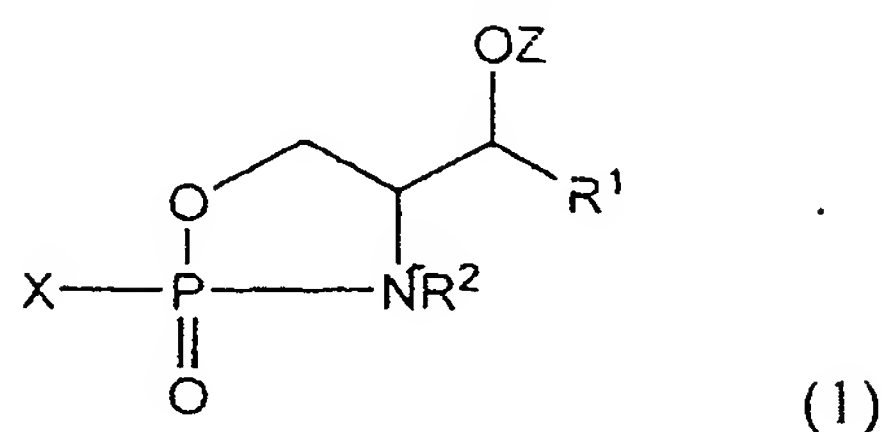
19. The process of Claim 18, wherein said phosphorylating reagent is POCl₃.

20. The process of any one of Claims 15 to 19, for the synthesis of the (*E*)-geometrical isomer of the compound of the following formula (1b):



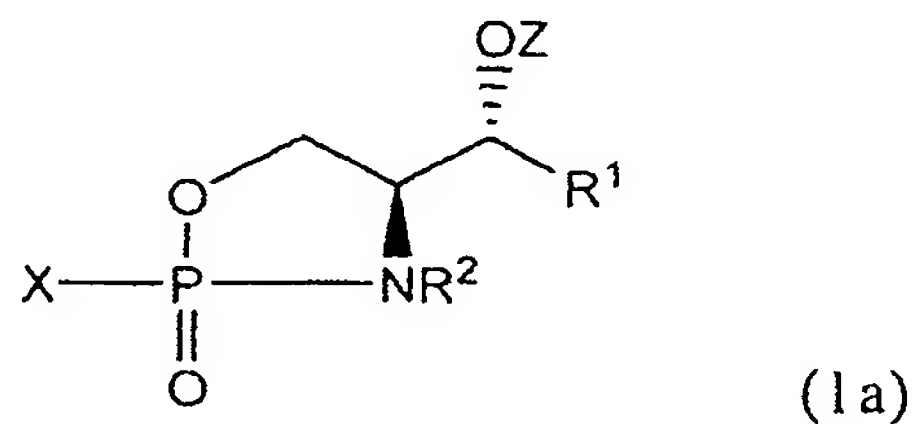
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21. An oxazaphospholane compound of the following formula (1):



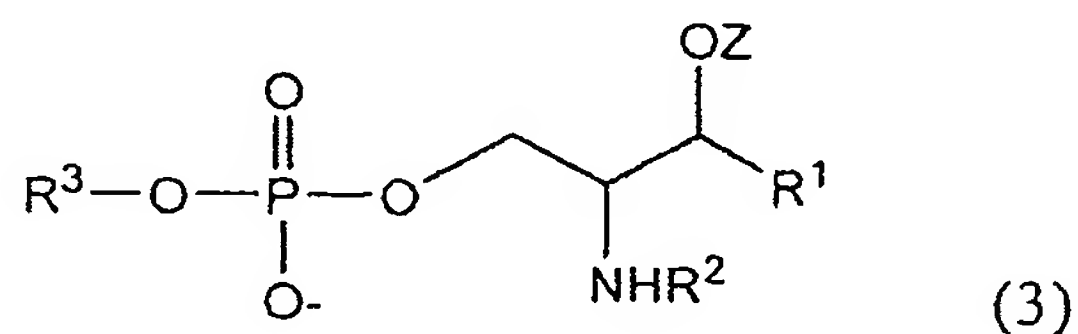
wherein R¹, R², Z and X are as defined in any one of Claims 1 to 14, obtainable by the process of any one of Claims 15 to 20.

22. An oxazaphospholane compound of the following formula (1a):



wherein R¹, R², Z and X are as defined in any one of Claims 1 to 14, obtainable by the process of any one of Claims 15 to 20.

23. A process making use of the oxazaphospholane of formula (1) as defined in any one of Claims 1 to 14, 21, and 22, for the manufacture of an acyclic oxazaphospholane derivative having the following formula (3):



wherein R¹, R² and Z are as defined, and R³ represent a hydrogen atom; an aliphatic moiety selected from aliphatic chain, amino aliphatic chain, heteroatom comprising aliphatic chain, aliphatic chain comprising a cyclic ring which ring may be saturated, partially saturated ring or an aryl group, said aliphatic chain may be branched or straight, saturated or unsaturated chain; or ether, polyether, or sugar moiety;

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the process comprises the step of reacting said oxazaphospholane of formula (1) with an alcohol or the formula R^3OH where R^3 is as defined, followed by treatment with an aqueous base or aqueous acid.

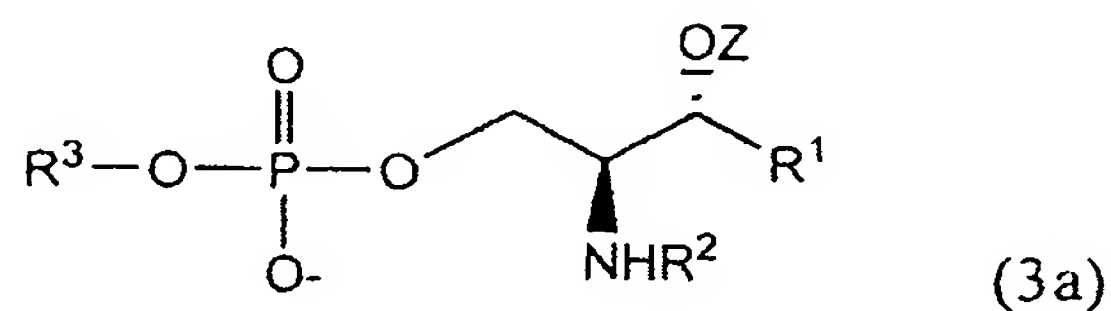
24. The process of Claim 23, wherein said alcohol is selected from choline, N-protected ethanolamines, oligoethyleneglycol monoethers, polyethyleneglycol monoethers, polyethers, or sugar moiety.

25. The process of Claim 24, wherein said alcohol is choline.

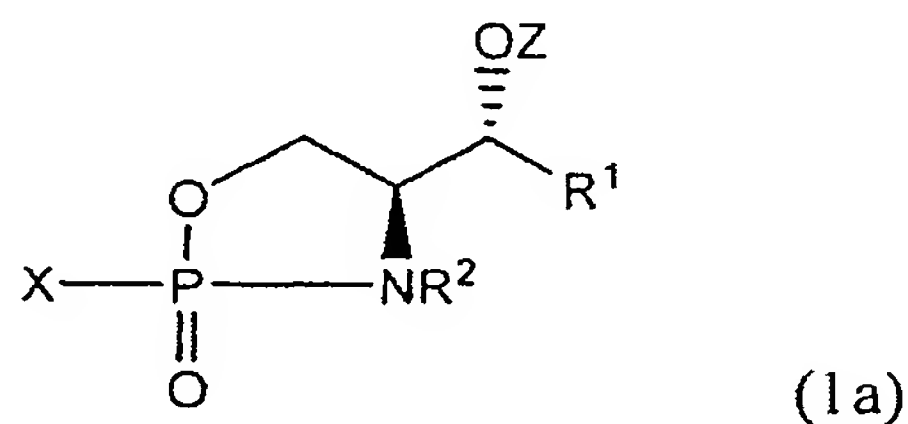
26. The process of any one of Claims 23 to 25, wherein said aqueous base is selected from trialkylamine, alkali metal- or alkali earth metal- hydroxide, carbonate or bicarbonate.

27. The process of any one of Claims 23 to 26, wherein said aqueous acid is a strong mineral acid or a Lewis acid.

28. The process of any one of Claims 23 to 27 for the manufacture of the 2S, 3R stereoisomer of formula (3a):



the process making use of a compound of formula (1a)

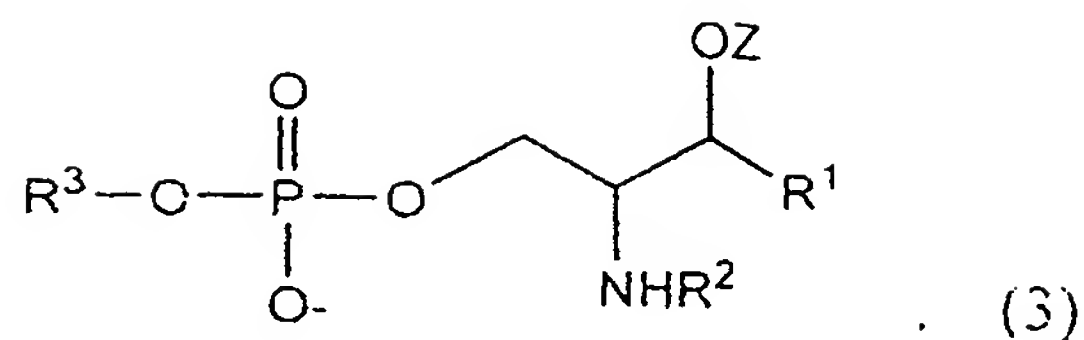


wherein R^1 , R^2 , R^3 , X and Z are as defined.

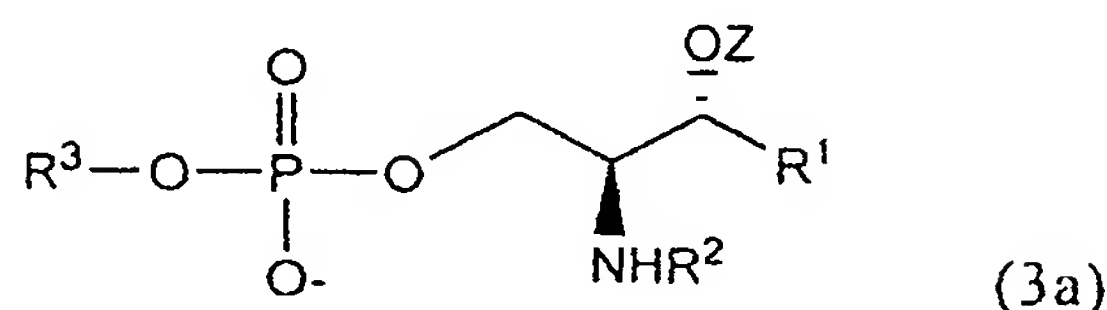
29. The process of any one of Claims 23 to 28, comprising reacting said compound of formula (3) or (3a) with a protecting group removing reagent to replace the protecting group Z with a hydrogen atom.

30. A phosphate derivative having the following formula (3):

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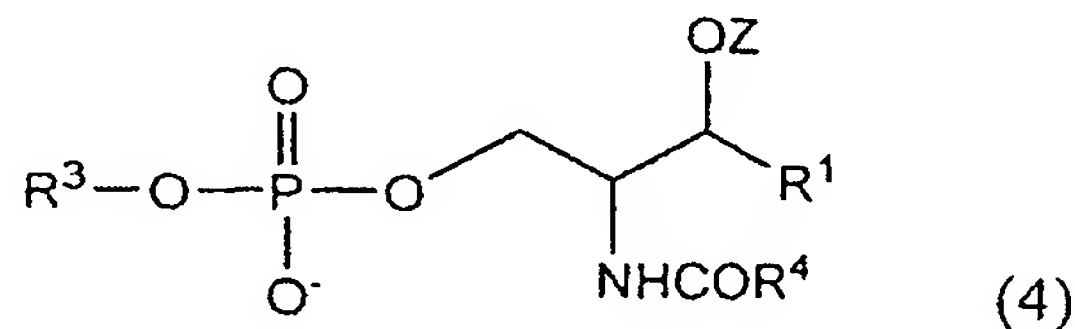


or its 2S, 3R stereoisomer of formula (3a):



obtained by the process of any one of Claims 23 to 29, wherein R^1 , R^2 , R^3 and Z are as defined.

31. A process making use of the oxazaphospholane of formula (1) as defined in any one of Claims 1 to 14, 21, and 22, wherein R^2 is a hydrogen atom, for the manufacture of a phosphate derivative having the following formula (4):



wherein R^1 , and Z are as defined, R^3 represent a hydrogen atom; an aliphatic moiety selected from aliphatic chain, amino aliphatic chain, heteroatom comprising aliphatic chain, aliphatic chain comprising a cyclic ring which ring may be saturated, partially saturated or aromatic ring, said aliphatic chain may be branched or straight, saturated or unsaturated chain; or an ether, polyether, or sugar moiety; and R^4 is hydrophobic group;

the process comprises

preparing a phosphate derivative of formula (3) according to any one of Claims 23 to 27;

reacting said phosphate derivative of formula (3) with an acyl compound of formula $\text{R}^4\text{C}(\text{O})\text{Q}$, wherein Q is a leaving group.

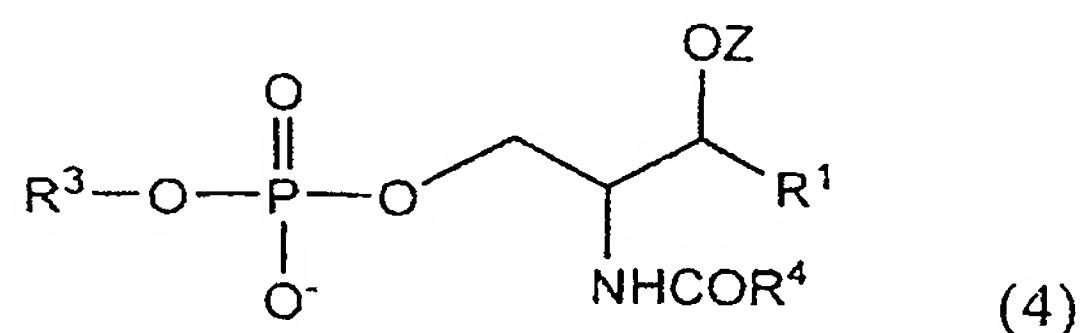
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32. The process of Claim 31, wherein said R^4 represents a C_1 - C_{24} aliphatic moiety selected from saturated or unsaturated, branched or linear aliphatic chain, said aliphatic chain optionally containing an aliphatic ring; the aliphatic chain or ring optionally substituted with one or more substituents containing a heteroatom selected from oxygen, halogen, nitrogen and sulfur.

33. The process of Claim 32, wherein said R^4 represents a saturated or unsaturated C_8 - C_{24} aliphatic chain.

34. The process of any one of Claims 31 to 33, for the manufacture of the 2S, 3R stereoisomer of the compound of formula (4), said process making use of the 2S, 3R stereoisomer of the compound of formula (1a).

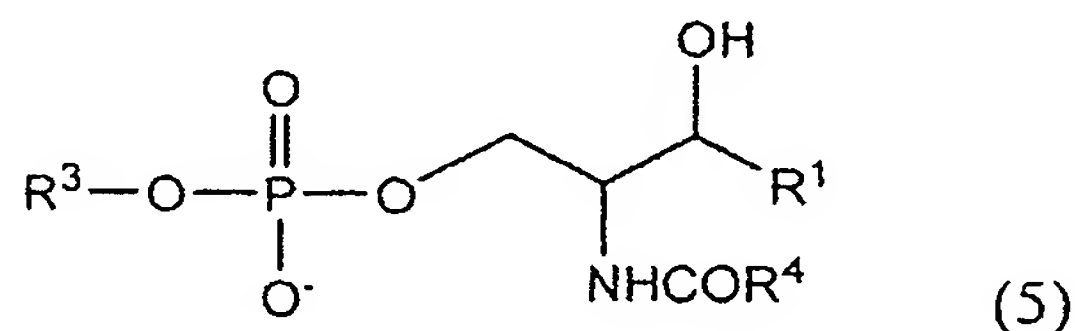
35. A phosphate derivative having the following formula (4):



or its 2S, 3R stereoisomer;

obtained by the process of any one of Claims 30 to 36, wherein R^1 , R^3 , R^4 and Z are as defined.

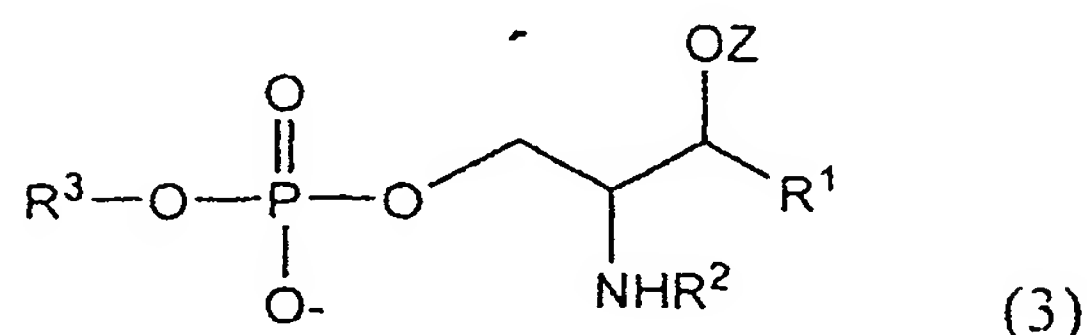
36. A process making use of the oxazaphospholane of formula (1) as defined in any one of Claims 1 to 14, 21, and 22, wherein R^2 is a hydrogen atom, for the manufacture of a sphingomyelin derivative having the following formula (5):



where R^1 and R^3 are as defined and R^4 is as defined in any one of Claims 31 to 34; the process comprises:

30

reacting said oxazaphospholane of formula (1) with an alcohol or the formula R^3OH where R^3 is as defined, followed by treatment with an aqueous base or aqueous acid to obtain a phosphate derivative having the following formula (3):



wherein R^1 , R^2 and Z are as defined, and R^3 represent a hydrogen atom; an aliphatic moiety selected from aliphatic chain, amino aliphatic chain, heteroatom comprising aliphatic chain, aliphatic chain comprising a cyclic ring which ring may be saturated, partially saturated ring or an aryl group, said aliphatic chain may be branched or straight, saturated or unsaturated chain; or ether, polyether, or sugar moiety;

reacting said phosphate derivative of formula (3) with an acyl compound of formula $R^4C(O)Q$, wherein Q is a leaving group and R^4 represents a C_1-C_{24} aliphatic moiety selected from saturated or unsaturated, branched or linear aliphatic chain, said aliphatic chain optionally containing an aliphatic ring; the aliphatic chain or ring optionally substituted with one or more substituents containing a heteroatom selected from oxygen, halogen, nitrogen and sulfur;

reacting said phosphate derivative of formula (4) with a protecting group removing agent to obtain a said sphingomyelin.

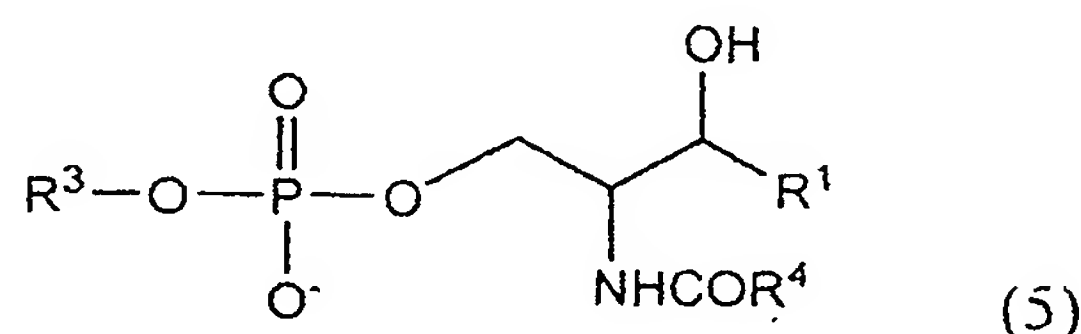
37. The process of Claim 36, for the manufacture of the 2S, 3R stereoisomer of the compound of formula (5), said process making use of the 2S, 3R stereoisomer of the compound of formula (1a).

38. The process of Claim 36 or 37, wherein Z in said compound of formula (4) is $Si(Ph_2)(t-Bu)$.

39. The process of any one of Claims 36 to 38, wherein said protecting group is removed by the use of hydrogen fluoride or $(R^6)_4NF$, wherein R^6 is a C_1-C_6 alkyl group.

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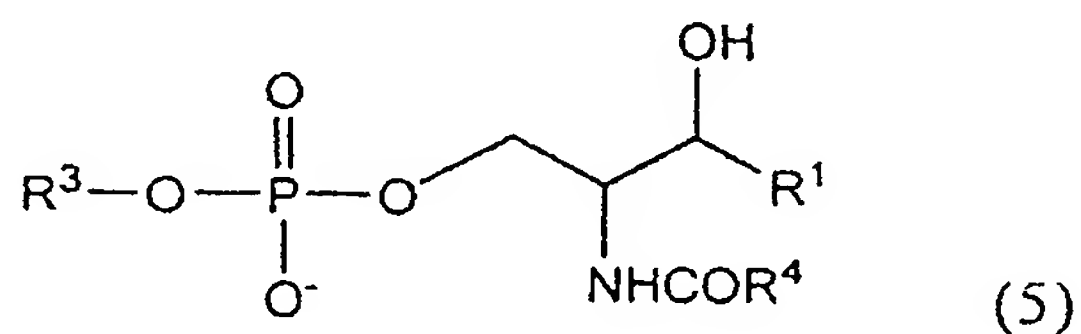
40. The process of Claim 39, wherein R^6 is n-butyl.
41. The process of any one of Claims 15 to 20, 23 to 29, 31 to 34 and 36 to 40 being a single pot process having as a starting material the compound of formulae (1), (1a), (2) or (2a).
42. The process of any one of Claims 36 to 41, for large scale production of said oxazaphospholane of formula (1) or (1a).
43. A sphingomyelin having the following formula (5):



or its 2S, 3R stereoisomer

obtainable by the process of any one of Claims 36 to 42, wherein said R^1 , R^3 and R^4 are as defined, provided that when said R^2 represents a C_{15} or C_{17} alkyl chain, R^1 cannot represent trans- $\text{CH=CHC}_{13}\text{H}_{27}$ and R^3 cannot represent $\text{CH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$.

44. A sphingomyelin having the following formula (5):

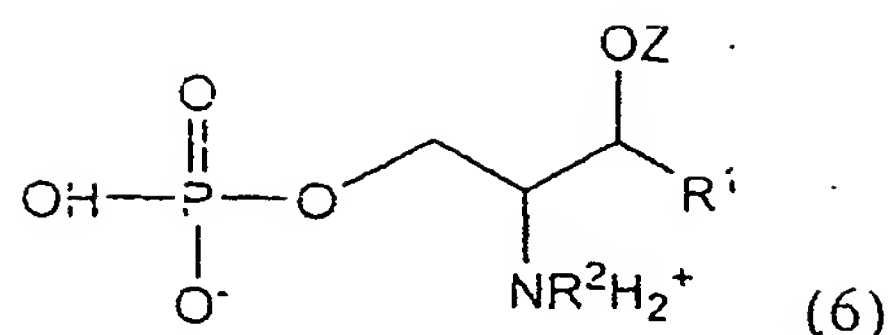


or its 2S, 3R stereoisomer

obtained by the process of any one of Claims 36 to 42, wherein said R^1 , R^3 and R^4 are as defined.

45. A process making use of the oxazaphospholane of formula (1) as defined in any one of Claims 1 to 14, 21, and 22, for the manufacture of a phosphate derivative having the following formula (6):

32



wherein R^1 , R^2 and Z are as defined, the process comprises reacting said oxazaphospholane of formula (1) with an aqueous base or an aqueous acid.

46. The process of Claim 45, for the manufacture of the 2S, 3R stereoisomer of the compound of formula (6), said process making use of the 2S, 3R stereoisomer of the compound of formula (1a).

47. The process of Claim 45 or 46, wherein said aqueous base is selected from trialkylamine, alkali metal- and alkali earth metal- hydroxide, carbonate or bicarbonate

48. The process of Claim 45 or 46, wherein said aqueous acid is a strong mineral acid or a Lewis acid.

49. A phosphate derivative having the formula (6), or (6a) obtained by the process of any one of Claims 38 to 41.

50. A pharmaceutical composition comprising a sphingomyelin according to Claim 43 or 44.

51. Use of a sphingomyelin according to Claim 43 or 44 for the preparation of a pharmaceutical composition.